IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

AMGEN INC., AMGEN MANUFACTURING, LIMITED; AND AMGEN USA, INC Plaintiffs, v. SANOFI; SANOFI-AVENTIS U.S. LLC; AVENTISUB LLC f/d/b/a AVENTIS PHARMACEUTICALS INC.; and REGENERON PHARMACEUTICALS, INC., Defendants.	)	Civ. No. 14-1317-SLR (Consolidated)

Melanie K. Sharp, Esquire and James L. Higgins, Esquire of Young Conaway Stargatt & Taylor, LLP, Wilmington, Delaware. Counsel for Plaintiffs. Of Counsel: William G. Gaede, III, Esquire, David L. Larson, Esquire, Eric W. Hagen, Esquire, Terry W. Ahearn, Esquire, Bhanu K. Sadasivan, Esquire, Sarah C. Columbia, Esquire, K. Nicole Clouse, Esquire, Lauren Martin, Esquire, Esther E. Lin, Esquire, Michael V. O'Shaughnessy, Esquire, and Rebecca Harker Duttry, Esquire of McDermott Will & Emery LLP.

Steven J. Balick, Esquire, Tiffany Geyer Lydon, Esquire, and Andrew C. Mayo, Esquire of Ashby & Geddes, Wilmington, Delaware. Counsel for Defendants. Of Counsel: Dianne B. Elderkin, Esquire, Steven D. Maslowski, Esquire, Matthew A. Pearson, Esquire, Angela Verrecchio, Esquire, Jenna M. Pellecchia, Esquire, Matthew G. Hartman, Esquire, and Jonathan J. Underwood, Esquire of Akin Gump Strauss Hauer & Feld LLP. John Josef Molenda, Esquire, Vishal Chandra Gupta, Esquire, Jeffrey C. Lee, Esquire, Siew Yen Chong, Esquire, Richard Praseuth, Esquire, and Robert Greenfeld, Esquire of Steptoe & Johnson LLP.

MEMORANDUM OPINION

Dated: January 3, 2017
Wilmington, Delaware

ROBINSON, District Judge

I. INTRODUCTION

On October 17, 2014, plaintiffs Amgen Inc., Amgen Manufacturing Limited, and Amgen USA Inc. (collectively "plaintiffs") brought this action alleging infringement of U.S. Patent Nos. 8,563,698; 8,829,165 ("the '165 patent"); and 8,859,741 ("the '741 patent") against defendants Sanofi, Sanofi-Aventis U.S. LLC, Aventisub LLC, and Regeneron Pharmaceuticals, Inc. (collectively "defendants"). (D.I. 1) Plaintiffs filed an amended complaint on November 17, 2014. (D.I. 10) Defendants answered the complaint on December 15, 2014. (D.I. 18, 19, 20) The court held a *Markman* hearing on September 17, 2015, and issued a claim construction order on October 25, 2015 construing certain disputed limitations of the '165 and '741 patents. (D.I. 151) On January 29, 2016, the court granted plaintiffs' motion to amend the complaint, which amended complaint was filed the same day consolidating into a single complaint plaintiffs' pleadings from four lawsuits (resulting in the addition of U.S. Patent Nos. 8,871,913; 8,871,914; 8,883,983; and 8,889,834). (D.I. 183, 184) Defendants answered the amended complaint on February 16, 2016. (D.I. 220) On February 22, 2016, defendants stipulated to infringement of the asserted claims of the patents-in-suit.[1] (D.I. 235) The court held a final pretrial conference on February 22, 2016.

The parties proceeded to trial on March 8, 2016, arguing the validity of the asserted claims. The court decided a series of evidentiary issues and *Daubert* motions before and during trial. (D.I. 226, 249, 250, 264, 269, 280) On March 16, 2016, the court granted defendants' judgment as a matter of law regarding willful infringement.

---

[1] Claims 2, 7, 9, 15, 19, and 29 of the '165 patent and claim 7 of the '741 patent.

(D.I. 302) On March 16, 2016, the jury returned a verdict finding the asserted claims of the patents-in-suit valid. (D.I. 304) Presently before the court are defendants' motions for a new trial and judgment as a matter of law on written description and enablement (D.I. 331, 332), and plaintiffs' motion to strike the opening brief in support of defendants' motion for judgment as a matter of law (D.I. 338). The court has jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331 and 1338(a).

II. BACKGROUND

A. Parties

Amgen Inc. and Amgen USA Inc. are corporations organized under the laws of the State of Delaware, with a principal place of business in Thousand Oaks, California. Amgen Manufacturing, Limited is a corporation organized under the laws of Bermuda with its principal place of business in Juncos, Puerto Rico. Sanofi is a company organized under the laws of France with its principal headquarters in Paris, France. Sanofi-Aventis U.S. LLC is a company organized under the laws of the State of Delaware with its principal place of business in Bridgewater, New Jersey. Aventisub LLC is a company organized under the laws of the State of Delaware having its principal place of business in Greenville, Delaware.[2] Regeneron Pharmaceuticals, Inc. is a corporation organized under the laws of the State of New York with its principal place of business in Tarrytown, New York. (D.I. 184 at ¶¶ 2-8, 12)

B. Technology

[2] Aventisub is the surviving entity from a June 2014 merger involving Aventis Pharmaceuticals Inc. and has assumed the assets, liabilities, and/or responsibilities of Aventis Pharmaceuticals Inc. Aventis Pharmaceuticals Inc. was a Delaware corporation having a principal place of business in Bridgewater, New Jersey.

1. The patents-at-issue

The '165 patent issued on September 9, 2014 and the '741 patent issued on October 14, 2014 (collectively "the patents-at-issue"). (JTX 2, 3) The patents-at-issue are titled "Antigen binding proteins to proprotein convertase subtilisin kexin type 9 (PCSK9)" and share a specification.[3] Proprotein convertase subtilisin kexin type 9 ("PCSK9") is a specific antibody involved in regulating the levels of the low density lipoprotein receptor ("LDLR") protein. (1:57-59) Monoclonal antibodies have a known "Y-shaped" structure made up of "two identical pairs of polypeptide chains," each pair having a heavy chain and a light chain. The carboxy-terminal portion of each chain typically defines a constant region. "The amino-terminal portion of each chain typically includes a variable region of about 100 to 110 or more amino acids that typically is responsible for antigen recognition." This allows different antibodies to bind to different antigens. (33:1-27) The specification describes monoclonal antibodies that bind to a specific region of PCSK9. (3:5-6)

The specification provides that 3000 human monoclonal antibodies were "rescreened for binding to wild-type PCSK9 to confirm stable hybridomas were established," and "a total of 2441 positives repeated in the second screen." (78:4-6, 35) Of these, "384 antibodies . . . blocked the interaction between PCSK9 and the LDLR well [and] 100 antibodies blocked the interaction strongly," "inhibit[ing] the binding interaction of PCSK9 and LDLR [at] greater than 90%." (80:22-26) The "screen of the 384 member subset identified 85 antibodies that blocked interaction between the PCSK9 mutant enzyme and the LDLR [at] greater than 90%." (80:35-37) The

[3] All references are to the '165 patent unless otherwise indicated.

specification provides the amino acid sequence of over two dozen of the identified antibodies. (Figures 2A-2D, 3A-3JJ, 15A-15D, 17:60-18:3, 20:1-8, 85:7-43) The specification describes the use of "epitope binning assays"[4] to characterize the different epitopes on PCSK9. 21B12 and 31H4 are representative members of two epitope bins that do not compete with each other for binding to PCSK9. (88:34-89:19) X-ray crystallography experiments were used to characterize the 21B12 and 31H4 binding sites. (99:56-103:60)

The claims reference specific amino acids at designated positions in SEQ ID NO: 1 and/or 3, which are specific amino acid sequences of PCSK9. (124-133) Claim 1 of the '165 patent recites:

> An isolated monoclonal antibody, wherein, when bound to PCSK9, the monoclonal antibody binds to at least one of the following residues: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of SEQ ID NO: 3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.

(427:47-52) Claim 1 of the '741 patent recites:

> An isolated monoclonal antibody that binds to PCSK9, wherein the isolated monoclonal antibody binds an epitope on PCSK9 comprising at least one of residues 237 or 238 of SEQ ID NO: 3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.

('741 patent, 427:36-40) At trial, defendants argued that the asserted claims were invalid for lack of written description and enablement and were obvious in light of the prior art.

2. Repatha™ and PRALUENT®

---

[4] Epitope binning assays are used to determine the ability of an antibody to block another's binding to the antigen. Antibodies with similar blocking profiles are grouped into a bin, indicating these antibodies bind to the same or overlapping epitopes. (88:34-89:37; D.I. 344 at 799:7-800:16)

Physicians recognize dyslipidemia caused by elevated LDL ("low density lipoprotein" or "bad" cholesterol) as a major risk factor for cardiovascular disease. Plaintiffs developed Repatha™ ("Repatha"), which uses an active ingredient "evolocumab" (identified as "21B12" in the specification). As described in the specification, evolocumab is a monoclonal antibody that targets PCSK9 to prevent it from engaging LDLR and ultimately lowers the levels of LDL in the blood. The FDA approved Repatha in August 2015. (D.I. 184; D.I. 342 at 241:15-24; D.I. 362 at 5) Defendants developed PRALUENT® alirocumab ("Praluent"), a monoclonal antibody that reduces LDL cholesterol levels in the blood. The FDA approved Praluent in July 2015. (D.I. 342 at 347:6-9, 350:23-351:5; D.I. 362 at 5)

III. STANDARDS OF REVIEW

A. Renewed Motion for Judgment as a Matter of Law

The Federal Circuit "review[s] a district court's denial of judgment as a matter of law under the law of the regional circuit. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1325 (Fed. Cir. 2016) (citation omitted). In the Third Circuit, a "court may grant a judgment as a matter of law contrary to the verdict only if 'the record is critically deficient of the minimum quantum of evidence' to sustain the verdict." *Acumed LLC v. Advanced Surgical Servs., Inc.*, 561 F.3d 199, 211 (3d Cir. 2009) (citing *Gomez v. Allegheny Health Servs., Inc.*, 71 F.3d 1079, 1083 (3d Cir. 1995)); *see also McKenna v. City of Philadelphia*, 649 F.3d 171, 176 (3d Cir. 2011). The court should grant judgment as a matter of law "sparingly," and "only if, viewing the evidence in the light most favorable to the nonmovant and giving it the advantage of every fair and reasonable inference, there is insufficient evidence from which a jury reasonably could find liability." *Marra v.*

Philadelphia Hous. Auth., 497 F.3d 286, 300 (3d Cir. 2007) (citing *Moyer v. United Dominion Indus., Inc.*, 473 F.3d 532, 545 n.8 (3d Cir. 2007)). "In performing this narrow inquiry, [the court] must refrain from weighing the evidence, determining the credibility of witnesses, or substituting [its] own version of the facts for that of the jury. *Id.* (citing *Lightning Lube, Inc. v. Witco Corp.*, 4 F.3d 1153, 1166 (3d Cir. 1993)). Judgment as a matter of law may be appropriate when there is "a purely legal basis" for reversal "that does not depend on rejecting the jury's findings on the evidence at trial." *Acumed*, 561 F.3d at 211.

B. Motion for a New Trial

Federal Rule of Civil Procedure 59(a) provides, in pertinent part:

> A new trial may be granted to all or any of the parties and on all or part of the issues in an action in which there has been a trial by jury, for any of the reasons for which new trials have heretofore been granted in actions at law in the courts of the United States.

Fed. R. Civ. P. 59(a). The decision to grant or deny a new trial is within the sound discretion of the trial court and, unlike the standard for determining judgment as a matter of law, the court need not view the evidence in the light most favorable to the verdict winner. *See Allied Chem. Corp. v. Daiflon, Inc.*, 449 U.S. 33, 36 (1980); *Leonard v. Stemtech Int'l Inc*, 834 F.3d 376, 386 (3d Cir. 2016) (citing *Olefins Trading, Inc. v. Han Yang Chem. Corp.*, 9 F.3d 282 (3d Cir. 1993)); *LifeScan Inc. v. Home Diagnostics, Inc.*, 103 F. Supp. 2d 345, 350 (D. Del. 2000) (citations omitted); *see also* 9A Wright & Miller, *Federal Practice and Procedure* § 2531 (2d ed. 1994) ("On a motion for new trial the court may consider the credibility of witnesses and the weight of the evidence."). Among the most common reasons for granting a new trial are: (1) the jury's verdict is against the clear weight of the evidence, and a new trial must be granted to prevent a

miscarriage of justice; (2) newly-discovered evidence exists that would likely alter the outcome of the trial; (3) improper conduct by an attorney or the court unfairly influenced the verdict; or (4) the jury's verdict was facially inconsistent. *See Zarow–Smith v. N.J. Transit Rail Operations*, 953 F. Supp. 581, 584-85 (D.N.J. 1997) (citations omitted). The court must proceed cautiously, mindful that it should not simply substitute its own judgment of the facts and the credibility of the witnesses for those of the jury. Rather, the court should grant a new trial "only when the great weight of the evidence cuts against the verdict and a miscarriage of justice would result if the verdict were to stand." *Leonard*, 834 F.3d at 386 (citing *Springer v. Henry*, 435 F.3d 268, 274 (3d Cir. 2006) and *Williamson v. Consol. Rail Corp.*, 926 F.2d 1344, 1352-53 (3d Cir. 1991)) (internal quotation marks omitted).

IV. MOTION FOR JMOL

A. Procedural Issue

Defendants renew their motion for JMOL on the issue of lack of written description and enablement, arguing that the evidence presented at trial was legally sufficient to show that the specification lacked written description and was not enabled. Plaintiffs challenge the propriety of the renewed motion as defendants did not formally move for JMOL under Rule 50(a) during trial. Fed. R. Civ. P. 50(a).

Rule 50(a) requires the movant to "specify the judgment sought and the law and facts that entitle the movant to judgment." Fed. R. Civ. P. 50(a). "The purpose of th[is] requirement is to afford the opposing party an opportunity to cure the defects in proof that might otherwise preclude the party from taking the case to the jury." *See Duro–Last, Inc. v. Custom Seal, Inc.*, 321 F.3d 1098, 1105 (Fed. Cir. 2003). The caselaw

indicates that a Rule 50(b) JMOL motion is properly founded where an oral Rule 50(a) motion was lodged; or a mere technical failure to comply with Rule 50(a) occurred, i.e., "the party clearly challenged the sufficiency of the evidence on the disputed issue at some point during trial, thereby alerting the opposing party as to the grounds on which the evidence is allegedly insufficient." *Id.* at 1106. The level of specificity required to give the opposing party notice has been the subject of interpretation, and may vary depending on the circumstances of the case. *See Fresenius Medical Care Holdings, Inc. v. Baxter Intern., Inc.*, 2007 WL 518804, *5 (N.D. Cal. Feb. 13, 2007) (collecting Federal Circuit authority).

At the close of defendants' case, on March 10, 2016, the court indicated that the parties should move on to the rest of the case postponing any motion practice until the jury was excused. (D.I. 343 at 720:17-19) After resolving an evidentiary issue outside the presence of the jury, the court stated that "if [plaintiffs] want to do [their] placeholder motion, [plaintiffs] should just say [that they] make a motion, and I will reserve judgment. No need to do much more than that." Plaintiffs moved for JMOL arguing that defendants did not present a sufficient evidentiary basis for a reasonable juror to find for defendants with respect to their invalidity defenses of obviousness, lack of written description, and enablement relating to the . . . asserted claims of the patents-in-suit." The court reserved judgment, and stated that there was "[n]o need for defendants to even respond" to plaintiffs' motion. (D.I. 343 at 725:15-726:8) On March 14, 2016, after further discussion with counsel, the court granted plaintiffs' motion for JMOL on obviousness. (D.I. 345 at 1076:21-1077:6) With this grant, the court issued a short instruction to the jury to explain why the testimony of plaintiffs' expert was cut off. (*Id.* at

1110:9-17) Plaintiffs then rested their case. Defendants did not formally move for JMOL on the issues of written description and invalidity and moved on to their rebuttal case. (*Id.* at 1100:18-23)

"The district court [is] in the best position to judge the sufficiency of [a] Rule 50(a) motion in the context of the trial . . . ." *Gaus v. Conair Corp.*, 363 F.3d 1284, 1287 (Fed. Cir. 2004). Throughout the trial, the crux of the invalidity dispute was defendants' contention of lack of written description and invalidity. Indeed, only these issues went to the jury (defendants having stipulated to infringement and the court having resolved the issue of willful infringement and obviousness). Under the circumstances, the court concludes that plaintiffs were apprised during trial of defendants' allegations of insufficient evidence of written description and enablement, therefore, defendants may proceed with the renewed JMOL.[5]

B. Standard

The statutory basis for the enablement and written description requirements, 35 U.S.C. § 112, provides in relevant part:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same . . . .

[5] In contrast, in *TruePosition Inc. v. Andrew Corp.*, 568 F. Supp. 2d 500 (D. Del. 2008) (cited by plaintiffs), the court found that defendant's pre-verdict JMOL motions regarding infringement (no offer for sale and failure of proof on claims 1 and 22) and damages, together with its counsel's statements, were insufficient to support the post-trial renewed JMOL motion on several other claims (willfulness; no lost profits damages based on the existence of non-infringing alternatives; government use; fraud; and promissory estoppel)).

35 U.S.C. § 112 ¶1. "The enablement requirement is met where one skilled in the art, having read the specification, could practice the invention without 'undue experimentation.'" *Streck, Inc. v. Research & Diagnostic Systems, Inc.*, 665 F.3d 1269, 1288 (Fed. Cir. 2012) (citation omitted). "While every aspect of a generic claim certainly need not have been carried out by the inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). The specification need not teach what is well known in the art. *Id.* (citing *Hybritech v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986)). A reasonable amount of experimentation may be required, so long as such experimentation is not "undue." *ALZA Corp. v. Andrx Pharmaceuticals, Inc.*, 603 F.3d 935, 940 (Fed. Cir. 2010).

"Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1378 (Fed. Cir. 2009) (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)). The Federal Circuit has identified several factors that may be utilized in determining whether a disclosure would require undue experimentation: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance disclosed in the patent; (3) the presence or absence of working examples in the patent; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability of the art; and (8) the breadth of the claims. *In re Wands*, 858 F.2d at 737. These factors are sometimes referred to as the "*Wands* factors." A court need not consider

every one of the *Wands* factors in its analysis, rather, a court is only required to consider those factors relevant to the facts of the case. *See Streck, Inc.*, 655 F.3d at 1288 (citing *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991)).

The enablement requirement is a question of law based on underlying factual inquiries. *See Green Edge Enterprises, LLC v. Rubber Mulch Etc., LLC*, 620 F.3d 1287, 1298-99 (Fed. Cir. 2010) (citation omitted); *Wands*, 858 F.2d at 737. Enablement is determined as of the filing date of the patent application. *In re '318 Patent Infringement Litigation*, 583 F.3d 1317, 1323 (Fed. Cir. 2009) (citation omitted). The burden is on one challenging validity to show, by clear and convincing evidence, that the specification is not enabling. *See Streck, Inc.*, 665 F.3d at 1288 (citation omitted).

A patent must also contain a written description of the invention. 35 U.S.C. § 112, ¶ 1. The written description requirement is separate and distinct from the enablement requirement. *See Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2011). It ensures that "the patentee had possession of the claimed invention at the time of the application, i.e., that the patentee invented what is claimed." *LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1344-45 (Fed. Cir. 2005). The Federal Circuit has stated that the relevant inquiry – "possession as shown in the disclosure" – is an "objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art. Based on that inquiry, the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed." *Ariad*, 598 F.3d at 1351.

This inquiry is a question of fact; "the level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Id.* (citation omitted). In this regard, defendant must provide clear and convincing evidence that persons skilled in the art would not recognize in the disclosure a description of the claimed invention. *See PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1306-07 (Fed. Cir. 2008) (citation omitted).

C. Evidence

1. 21B12 and 31H4

The parties agreed that the patent described the screening of about 3,000 antibodies to determine which ones block the binding of PCSK9 to the LDL receptor. The inventors chose 384 antibodies, which blocked PCSK9 "well" for further testing. Of these, 100 antibodies were identified that blocked PCSK9 at over 90%. (D.I. 342 at 283; D.I. 343 at 637:18-639:3, 742) The parties also agreed that the patents-in-suit disclose two antibodies (21B12 and 31H4) that bind to a specific region (the "binding region") of PCSK9.[6] The inventors identified the binding region using X-ray crystallography of 21B12 and 31H4. (D.I. 342 at 283-286:11, 411:4-9, 415:15-21; D.I. 343 at 550:7-17; D.I. 344 at 881:19-882:4, 916:6-8) The specification only provides X-ray crystallography data for 21B12 and 31H4. (D.I. 342 at 283:10-14; D.I. 343 at 645:4-13; D.I. 344 at 882:5-8, 937:24-938:6)

2. Defendants' evidence

---

[6] The court will refer to this region as "the binding region," rather than the list of names used by the various witnesses including, but not limited to: region, zone, hot zone, central patch, patch, specific area, and sweet spot.

Defendants' expert, Dr. Michael Eck ("Dr. Eck"), testified that the patent disclosed the topography of PCSK9 and the fifteen residue binding region, as well as the crystal structure. (D.I. 343 at 562:19-563:4, 579:1-11; *see also* D.I. 344 at 633:22-634:22, 676:2-677:10) He explained that 21B12 and 31H4 "bind to very defined spots on the surface of PCSK9, [21B12] on one spot, sort of at the edge . . . of the [binding] region [and] 31H4 on the opposite edge." (D.I. 343 at 540:9-541:2; D.I. 345 at 1114:5-1116:13) He stated that 21B12 "probably interacts with probably eighteen amino acids on the surface," four of which are in the binding region. 31H4 interacts with about thirty amino acids total and three in the binding region. (D.I. 343 at 556-557) There are residues in the "middle" of the binding region that are not bound by either 21B12 or 31H4. (D.I. 343 at 546:4-19, 556:4-557:4; D.I. 345 at 1115:10-13) He opined that there are "many different positions on the surface of PCSK9, including this region in the middle, where one would expect antibodies to [be] able to bind, and we see here in [plaintiffs'] patent exactly two examples of antibodies that we know bind in this general vicinity, both on the edge." (D.I. 343 at 541:3-10) There is no example of an antibody "that interacts with the middle and binds [S]153 or likewise D238 or I369 or V380." (D.I. 345 at 1118:14-1119:12) Defendants' other expert, Dr. Donald Siegel ("Dr. Siegel"), similarly concluded that the patents-in-suit do not show the structure of an antibody that binds centrally to the binding region and opined that such an antibody "would have to have a different amino acid sequence or structure than either" 21B12 or 31H4. Moreover, it "would be interacting in a different way." (D.I. 343 at 634:6-25, 645:14-24)

Dr. Eck further explained that there are other possible antibodies, which would have different structures and mechanisms of binding with the binding region. Such

antibodies "[m]ight interact with many of the same residues on PCSK9, but [also with] a few different residues." That a certain antibody binds to a particular amino acid on PCSK9 "does not tell you anything at all about the structure," "only about its function." Moreover, there are no developed methods for working back from a binding target "to reliably predict how to make an antibody to bind there." (*Id.* at 547:18-549:16, 564:14-17) Nor can one predict where an antibody would bind on PCSK9 from its structure. (*Id.* at 558:6-9, *see also* 684:3-18) For example, one would expect that "many antibodies with very different chemical structures could bind to PCSK9 and" bind to "D238, but do it in very different ways, with many different antibody structures." (D.I. 343 at 580:11-22, 587:20-588:3, 588:18-590:5)

Dr. Eck testified that the specification disclosed eleven other antibodies that have essentially the same sequence as 21B12. He opined that if the multiple copies of 21B12 are "binding at all, they have to be binding right where [21B12] is." (D.I. 343 at 558:12-559:1) Dr. Eck also testified that there are "on the order of thousands of different versions of . . . 21B12," and the patent does not describe any "examples of antibodies that bind centrally across the middle" of the binding region. (D.I. 345 at 1112:24-1113:19) Dr. Eck briefly described that an antibody may "contact" an amino acid without binding to the amino acid, such that 21B12 contacts the middle amino acid of the EGF-A region (the region of the LDL receptor that binds and interacts with PCSK9). (D.I. 343 at 557, 565:1-18)

Yet another of defendants' experts, Dr. Jeffrey Ravetch ("Dr. Ravetch"), testified that the antibody technology was extremely well developed and a "mature technology." The use of "transgenic mice and phage display," as well as other laboratory methods,

were routine techniques. (D.I. 342 at 409:7-11, 413:3-20, 414-415) Dr. Siegel explained that the asserted claims were not limited to human antibodies, but could be mouse or camel antibodies. The structures of such non-human antibodies would be "much different" than human antibodies. (D.I. 343 at 632:20-633:12) He also explained that the asserted claims (excepting claim 29 of the '165 patent) do not specify a particular level of blocking, such that "any small amount of blocking would define an antibody that fit in the genus of antibodies." (*Id.* at 632:15-19)

Dr. Eck explained that to determine similarities of antibodies, a person of ordinary skill considers "their chemical structure, their composition, their primary amino acid sequence and their three-dimensional structure." (*Id.* at 577:21-578:4) He concluded that there are "many antibodies that will meet [the asserted] claims that have nevertheless very diverse and different three-dimensional structures and primary amino acid sequences." He could not "visualize or recognize" these based on the teachings of the specification. Further, "having the expectation that there are many antibodies that will bind [to the binding region] is different than being able to know precisely what those structures are and to be able to realize and make and use any of those structures." (*Id.* at 583:13-584:14) The specification does not offer "clear evidence" of antibodies binding to the "many ways one could have antibodies binding, covering this central region, as well, for example, as binding to the north edge, or binding to the south edge." (D.I. 345 at 1117:2-21)

Dr. Siegel explained that the claims of the patents-in-suit "are very broad" and "cover a large number of antibody structures, not limited in any way." He opined that the specification does not "provide a description of [the] invention." (D.I. 343 at 612:9-

17) Moreover, the claims reciting an antibody that binds to at least one residue (for example D238), do not provide information about the structure or sequence of such antibody. (*Id.* at 630:9-12) He testified that there are no "common structural features . . . described that would make one understand . . . the structures of other antibodies." (*Id.* at 659:3-22) Dr. Siegel concluded that the two antibodies are not representative of antibodies that would bind in the middle of the binding region. (*Id.* at 650:24-651:10) He also opined that the 20 or more sequences reported in the specification are insufficient to represent the diversity of antibodies covered by the asserted claims. (*Id.* at 707:18-22)

As to the enablement requirement, Dr. Siegel testified that it would not be possible to start with the amino acid sequences listed in the specification and make "the full diversity of antibodies that are covered by the claims," because "[i]t's a very unpredictable process" and would require trial and error. (*Id.* at 662:19-663:10) He stated that the methods were known (*id.* at 664-668:9) but, in his opinion, the process would involve undue experimentation, as "there are a lot of steps involved" and there is nothing in the specification to help a researcher "hone in on an antibody that satisfies the claims." (*Id.* at 668:10-669:13) The specification has not disclosed a "quick way of doing" the research, or "taught . . . anything special." (*Id.* at 701:4-8) That the binding region is known is not useful in making the antibodies, as the antibodies must be made and tested to determine where they bind. (*Id.* at 672:22-673:20, 714:10-12) He stated that "even today, we're talking about how immature the art is where you can't take an antigen and figure out how to make an antibody that will bind to it." (*Id.* at 695:5-9)

3. Plaintiffs' evidence

Plaintiffs' scientific director, Dr. Simon Jackson ("Dr. Jackson"), testified that the crystallography data "showed . . . the specific amino acids that were . . . binding" and "that the antibodies were binding in a small region side by side on PCSK9." (D.I. 342 at 285) Plaintiffs' expert, Dr. Gregory Petsko ("Dr. Petsko"), testified that when the antibodies bind, they cover "a footprint." (D.I. 344 at 799) Dr. Petsko disagreed with the characterization of 21B12 and 31H4 as "edge binders." He described the antibodies as "very large objects" with "a pretty big footprint on the" binding region, that "don't really hang onto the edge at all." (*Id.* at 805) He explained that the 15 residues that constitute the binding region are covered "virtually perfectly, including . . . [F]379" by 21B12 and 31H4. (*Id.* at 806) On cross-examination, Dr. Petsko was asked: "Based on the information available in the patent as of January 9, 2008, one cannot determine that any of the antibodies disclosed bind to PCSK9 in between where 21B12 and 31H4 bind; is that correct?" He explained that "when a scientist hears the word 'determined,' a scientist often thinks about doing experiments." He responded that without experiments, however, he didn't "know for sure that there are any such antibodies." (*Id.* at 862:19-863:15)

Dr. Petsko testified that example 11 in the patent describes the blocking data for the antibodies, i.e., the ability of the antibody to prevent the LDL receptor from binding to PCSK9. Example 3 of the patent discloses that the inventors were in possession of 85 antibodies that blocked at more than 90%. He explained that the 384 member subset blocked quite reasonably. (*Id.* at 796-797) Dr. Jackson explained that "[b]inning is a way to group antibodies . . . depending on how they bind and where they bind to the protein, in this case PCSK9." (D.I. 342 at 267) Antibodies that co-bin cannot bind "at

the same time," instead they "compete against each other for binding to the site." (*Id.* at 269) The specification uses 21B12 as a representative antibody for bin 1 and 31BH4 for bin 3. (D.I. 344 at 270) Dr. Petsko testified that "binning experiments . . . tell you whether antibodies have overlapping footprints on the surface of PCSK9." (*Id.* at 798:15-17) He explained that bin 1 (containing seventeen antibodies) and bin 3 (containing seven antibodies) "represent the collection of antibodies that co-bin with 21B12 and the collection that co-bin with 31H4," respectively.[7] (*Id.* at 798-802)

Chadwick King ("King"), one of the named inventors on the patents-in-suit, testified that the screening process used in the patent allowed plaintiffs to "identify . . . antibodies that are highly active, have a function of interest, but also have sequence diversity." Sequence diversity helps ensure that there are "enough molecules [so] that one of them can potentially make it through the later stage steps of drug development . . . [and] testing." He opined that the panel of thirty antibodies "had nice sequence diversity" and "cover[ed] multiple epitopes." He concluded that "comparisons of [the] antibody sequences to the germline consensus region" resulted in "good diversity in germline usage." (D.I. 343 at 744-746)

According to Dr. Petsko, 21B12 and 31H4 are sufficiently representative of the asserted claims, as they provide "all the information" needed "to define the part of PCSK9 where the antibodies need to bind in order to block." (D.I. 344 at 806-807, 811) He described generally how an antibody comes together with PCSK9 and that there are different types of chemical interactions possible with an amino acid (for example D238).

---

[7] Dr. Siegel answered a short series of questions regarding co-binning on cross examination, and conceded that the "epitopes would overlap if [the antibodies] co-bin." (D.I. 343 at 688:14-691:25)

(*Id.* at 808-809) Dr. Petsko agreed that antibodies could have different kinds of chemical interactions with a particular residue, but disagreed with the characterization that such differences result in a significant difference in structure. (*Id.* at 808:24-809:23) Using S153 as an example, Dr. Petsko described "the noncovalent interaction that contributes to the affinity of the antibody for PCSK9." (*Id.* at 815-16) He reasoned that 21B12 binds to S153, R194, R237, D238, D374, T377, and F379 and, therefore, falls within the scope of claims 2, 7, 19, and 29 of the '165 patent and claim 7 of the '741 patent. 31H4 binds to D374 and V380, with a possibility of binding to S381 and, therefore, falls within the scope of claims 15, 19, and 29 of the '165 patent.[8] (*Id.* at 817)

Dr. Petsko explained that using the binning and blocking data, it is "more likely than not that one or more of those [antibodies] are going to make interactions with the residues" of the binding region. He identified which of the co-binned antibodies identified in the patent would "more likely than not" meet the claim limitations of claims 19 and 29 of the '165 patent. (*Id.* at 818-21, 824-25, 827) He opined that although the specification does not disclose "a crystal structure [for] an antibody that binds to I369," the inventors were in possession of such an antibody, because the patent discloses a list of "strong blockers," which would contain antibodies that are likely to bind I369. (*Id.* at 830-32) In other words, the "inventors are in possession of a large number of antibodies and we've described two that cover quite a bit of the [binding region], and we've also indicated the likely presence of antibodies that will interact with even more residues in the [binding region]." (*Id.* at 831-32)

[8] Dr. Eck disagreed with the detail of Dr. Petsko's analysis (but can "understand where he's coming from") that 21B12 and 31H4 interact with D374. (D.I. 345 at 1120:5-10)

Dr. Petsko testified that, although one could not sit at a desk and write out all the sequences, a scientist would use the information provided to find antibodies that bind to the binding region on PCSK9. (*Id.* at 836:5-837:14) The specification provided sufficient information to conclude that 21B12 and 31H4 are representative. (*Id.* at 818-819) On cross-examination, Dr. Petsko agreed that there could be "many antibodies that recognize the same epitope," and the specification does not provide "the formula" for all of them, but added that "nobody could do that." (*Id.* at 869:14-23) He also conceded that whether an antibody would bind with a particular residue is "not certain at all" from co-binning data. (*Id.* at 880-881, *see also* D.I. 343 at 594:23-595:6, 600:22-601:3) Dr. Jackson concluded that using the X-ray crystallography of 21B12 and 31H4 and the binning data, plaintiffs "knew that the other antibodies were binding in" the binding region. (D.I. 342 at 291-292)

Another of plaintiffs' experts, Dr. Anthony Rees ("Dr. Rees"), also described using binning data to make antibodies and screening them against 21B12 to see if they compete. (D.I. 344 at 917-18) He testified that, from a scientific perspective, making additional antibodies did not require undue experimentation. With "a particular series of steps . . . to follow," it is "routine experimentation with some surprises along the way, but which [a person of ordinary skill] can solve in routine ways." (*Id.* at 920) He evaluated the diversity of the patent's antibodies and concluded that the sequences, which lead to differences in protein sequence and structure, result in "seven different families." He reasoned that this was "quite an extensive diversity." (*Id.* at 923-26) He concluded that a skilled person in the art "would understand that [plaintiffs'] antibodies are representative of the" antibodies of claim 19, based on the disclosure of "detailed three-

dimensional structure" of 21B12 and 31H4, and the twenty-two "other antibodies that are disclosed with respect to their competition or their binning behavior." (*Id.* at 937:17-938:6)

As to a structure-function relationship, Dr. Petsko opined that antibodies can bind through "noncovalent interactions," which "hold them together more often than not." (*Id.* at 791-92) He explained that a "different amino acid sequence might approach a particular residue from a different direction . . . to make a noncovalent interaction with the residue," but this does not affect the structure-function relationship. (*Id.* at 838-40) Dr. Petsko concluded that the specification describes a structure-function relationship by "describing structure characteristics that the antibodies in the genus have in order to carry out the function of binding to PCSK9, blocking the binding of the LDL receptor." More specifically, the "structure function relationship is binding to specific residues on the" binding region. (*Id.* at 783:25-784:19) The specification provides a person of skill in the art the ability to visualize and recognize antibodies falling within the claims based on crystal structures and binning experiments. (*Id.* at 836:22-837:23)

Dr. Rees opined that when an antibody binds to PCSK9, it takes on a unique structure and precisely fits together. So "all the antibodies . . . that bind to this region must share structural features . . . that allow them to get the shape fitting that is required." (*Id.* at 908:10-24, 902:22-903:14, 905:23-906:10) For example, two different amino acid sequences, which bind to the antigen region from influenza may have a different structure, but still share the structural feature of binding to the region. (*Id.* at 910:13-911:18) The "antibodies that fall within the scope of the claims have common structural features." These structural features lead "to the functions of binding and

blocking" in order to block the binding of PCSK9 to its LDL receptor. "[T]he consequence of that is there must be a correlation between structure and function." (*Id.* at 912:8-22) On cross-examination, Dr. Rees agreed that the amino acid sequences defined the antibody and the detailed interactions of the amino acids lead to the folded structure. (*Id.* at 986:9-24)

As to the well characterized antigen test, Dr. Petsko testified that he used the term antigen to describe the binding region (part of PCSK9) and that the binding region could be considered a "newly characterized antibody." Dr. Petsko explained how to design more antibodies from the disclosures in the patent – by using 21B12 as a reference, performing binning experiments, testing to see whether the antibodies block the binding to the LDL receptor, and then using developed techniques to screen the antibodies. (*Id.* at 834:17-836:4, 871:10-20; *see also* 915:13-922:24, 937:11-16)

As to enablement, Dr. Rees testified that the state of antibody and engineering sciences is "mature and well established," with well-known methods for creating antibodies, such as those described in the specification. In his opinion, the scope of the claims "is pretty narrow," as they describe "antibodies that bind to a rather small region on the surface of PCSK9." He opined that the specification is a "comprehensive roadmap to how to make . . . [the] antibodies." (*Id.* at 940-41; *see also* D.I. 342 at 401:23-402:7, 417:10-21) He explained that a researcher does not use the binding region to make the antibodies, but the specification teaches "how to analyze for antibodies that bind to" it. (D.I. 344 at 942) Dr. Rees explained that other types of antibodies are well known, including mouse monoclonal antibodies, rat antibodies, and camel antibodies. Moreover, those types of antibodies, as well as fragments, may be

made using the information in the specification and routine methods known in the art. (*Id.* at 942-43) On cross-examination, Dr. Rees agreed that the examples of the specification did not describe mouse or camel antibodies. (*Id.* at 981:21-982:12) As to the degree of blocking, Dr. Petsko opined that if an antibody bound to one of the residues, it would be likely that "the big molecule" (with a "pretty big footprint") would cause some blocking. Moreover, the patent disclosed certain "low blocking" antibodies. (*Id.* at 840:5-25) Dr. Petsko agreed that a small amount of blocking would suffice to meet the requirements of certain of the asserted claims. (*Id.* at 870:11-24)

D. Analysis

The jury was asked to consider whether defendants presented clear and convincing evidence that the asserted claims of the patents-in-suit lacked written description and enablement. The court instructed the jury that the specification could disclose either "a representative number [of] species falling within the scope of the claimed invention," or "structural features common to the members of the genus, so that a person of ordinary skill in the art can 'visualize or recognize' the members of the claimed invention." The jury was also instructed that "[i]n the case of a claim to antibodies, the correlation between structure and function may also be satisfied by the disclosure of a newly-characterized antigen by its structure, formula, chemical name, or physical properties if" the creation of such "antibodies against such an antigen was conventional or routine." (D.I. 299 at 24-25)

The parties and their experts largely agreed on what the specification discloses – a screening process used to select 384 antibodies, which blocked PCSK9 "well" for further testing; a certain subset of antibodies that blocked PCSK9 at over 90%; two

antibodies (21B12 and 31H4), which underwent X-ray crystallography analysis; a binding region on PCSK9 of fifteen residues that is the target of such antibodies. The parties' experts also agreed that the art discloses the research techniques necessary to perform antibody development and screening.

The parties' experts analyzed the specification's disclosures and formulated conclusions. Defendants' experts focused on the "middle" portion of the binding region and concluded that insufficient data and examples were disclosed in the specification. Plaintiffs' experts argued the opposite, that is, the examples and disclosures in the patent sufficiently described two antibodies which bind to a large portion of the binding region. An antibody that would bind to the part of the binding region that is not specifically bound by 21B12 and 31H4 is logically within reach using the disclosures of the specification (including the blocking and binning data).

The jury is the finder of fact and is tasked with weighing the evidence and credibility of the witnesses. The parties' experts provided the jury with competing testimony on the interpretation of the data available in the specification. The jury concluded that the asserted claims were not invalid for lack of written description or enablement. Defendants' post-trial arguments essentially ask the court to reevaluate the experts' testimony and reach the opposite conclusion. For example, defendants argue that the two antibodies (21B12 and 31H4) are "plainly insufficient" to represent the genus, and the twenty-two other antibodies that "bin" with 21B12 and 31H4 are not value added as "binning does not allow a person of ordinary skill in the art to determine with any certainty what amino acid an antibody binds to." According to defendants, their experts testified that "nothing disclosed in the [specification] allowed one to visualize or

recognize the structures of the claimed antibodies and to distinguish the claimed antibodies from others." According to defendants, plaintiffs' experts "gave purely conclusory testimony" that the specifications did allow such visualization or recognition. (D.I. 367 at 7, 15)

On the record at bar, plaintiffs' experts provided more than conclusory testimony in order to explain their respective conclusions to the jury. The jury credited such testimony over that of defendants' experts. The court declines to re-weigh the evidence or the credibility of the experts. Viewing the record in the light most favorable to plaintiffs, substantial evidence supports the jury's verdict.[9, 10] For these reasons, defendants' renewed motion for JMOL is denied.

In the alternative, defendants requested a new trial should the court deny the renewed motion for JMOL on written description and enablement. Defendants' request is premised on the same arguments as its renewed motion for JMOL. Defendants again ask the court to "substitute its own judgment of the facts and the credibility of the witnesses," and reach the opposite conclusion as the jury. For the reasons discussed

---

[9] Defendants argue that *Regents of the Univ. of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997), requires a finding that the disclosure is insufficient to meet the representative species test. However, the procedural posture of that case, as well as the facts, are different. Reviewing the district court's findings following a bench trial, the Federal Circuit held that the written description requirement was not met. It reasoned in part that the specification disclosed "only a general method for obtaining the human cDNA (it incorporates by reference the method used to obtain the rat cDNA) along with the amino acid sequences of human insulin A and B chains. Whether or not it provides an enabling disclosure, it does not provide a written description of the cDNA encoding human insulin." *Id.* at 1567.

[10] The jury's verdict is supported by the evidence on the "representative number of species" or "common structural features" tests, therefore, whether the jury credited the evidence on the "well-characterized antigen" test is not dispositive.

above, the jury's verdict is not against the clear weight of the evidence, therefore, the court denies defendants' request for a new trial.

V. RECONSIDERATION

In their motion for a new trial, defendants argue that the erroneous exclusion of post-January 2008 evidence substantially prejudiced their defenses of lack of written description and enablement; the jury was erroneously instructed on the test for written description (with respect to the court's "well-characterized antigen" instruction); and the court's grant of JMOL as to obviousness was based on an erroneous interpretation and misapplication of *Dynamic Drinkware v. National Graphics*, 800 F.3d 1375 (Fed. Cir. 2015). While filed as part of a motion for a new trial, defendants essentially request reconsideration of each of the above issues.

A motion for reconsideration is the "functional equivalent" of a motion to alter or amend judgment under Federal Rule of Civil Procedure 59(e). *See Jones v. Pittsburgh Nat'l Corp.*, 899 F.2d 1350, 1352 (3d Cir. 1990) (citing *Fed. Kemper Ins. Co. v. Rauscher*, 807 F.2d 345, 348 (3d Cir. 1986)). The standard for obtaining relief under Rule 59(e) is difficult to meet. The purpose of a motion for reconsideration is to "correct manifest errors of law or fact or to present newly discovered evidence." *Max's Seafood Cafe ex rel. Lou-Ann, Inc. v. Quinteros*, 176 F.3d 669, 677 (3d Cir. 1999). A court should exercise its discretion to alter or amend its judgment only if the movant demonstrates one of the following: (1) a change in the controlling law; (2) a need to correct a clear error of law or fact or to prevent manifest injustice; or (3) availability of new evidence not available when the judgment was granted. *See id.* A motion for reconsideration is not properly grounded on a request that a court rethink a decision

already made and may not be used "as a means to argue new facts or issues that inexcusably were not presented to the court in the matter previously decided." *Brambles USA, Inc. v. Blocker*, 735 F. Supp. 1239, 1240 (D. Del. 1990); *see also Glendon Energy Co. v. Borough of Glendon*, 836 F. Supp. 1109, 1122 (E.D. Pa. 1993). It goes without saying, therefore, that a motion under Rule 59(e) that advances the same arguments already thought through and rejected by the court - rightly or wrongly - should be denied. *See, e.g., Lazaridis v. Wehmer*, 591 F.3d 666, 669 (3d Cir. 2010); *Savage v. Bonavitacola*, 2005 WL 730679 (E.D. Pa. Mar. 29, 2005), at *1 (citing *Glendon Energy Co. v. Boroough of Glendon*, 836 F. Supp. 1109, 1122 (E.D. Pa. 1993)); *Brambles USA, Inc. v. Blocker*, 735 F. Supp. 1239, 1240 (D. Del. 1990).

As to the exclusion of post-January 2008 evidence, the complexity of the matter mandated that the court draw lines and stick to them. (D.I. 345 at 1076:6-1077:25) The court entertained both argument and briefing on this dispute, and issued written orders in support of its decision. (D.I. 226, 249) As to the inclusion of the "well-characterized antigen" jury instruction (D.I. 299 at 25), again the parties were provided opportunity to present argument and briefing, which the court considered. (D.I. 291; D.I. 344 at 1063:5-1065:21) As to the courts' grant of JMOL on obviousness, the court fully considered defendants' arguments as to the applicability of the *Drinkware* case, both before and during trial. (D.I. 250, 282; D.I. 345 at 1076:21-1077:6, 1089:14-17) While defendants disagree with the court's decisions and request that it rethink them, the court declines to do so. The court did not arrive at any of these decisions lightly; indeed, it considered fulsome arguments and briefing. Defendants' request for reconsideration of these issues is denied, as is the motion for a new trial.

For the foregoing reasons, the court denies defendants' motions for a new trial and judgment as a matter of law on written description and enablement (D.I. 331, 332); and denies as moot plaintiffs' motion to strike the opening brief in support of defendants' motion for judgment as a matter of law (D.I. 338). An appropriate order shall issue.

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

AMGEN INC., AMGEN MANUFACTURING, LIMITED; AND AMGEN USA, INC Plaintiffs, v. SANOFI; SANOFI-AVENTIS U.S. LLC; AVENTISUB LLC f/d/b/a AVENTIS PHARMACEUTICALS INC.; and REGENERON PHARMACEUTICALS, INC., Defendants.	)	Civ. No. 14-1317-SLR (Consolidated)

ORDER

At Wilmington this 3rd day of January 2017, consistent with the memorandum opinion issued this same date;

IT IS ORDERED that:

1. Defendants' renewed motion for judgment as a matter of law on written description and enablement (D.I. 332) is denied.

2. Defendants' motion for a new trial (D.I. 331) is denied.

3. Plaintiffs' motion to strike the opening brief in support of defendants' motion for judgment as a matter of law (D.I. 338) is denied as moot.

United States District Judge